

MARKED UP SPECIFICATION

Delete the first full paragraph of page 6, starting at line 6, and insert the following therefor:

Under these circumstances, an object of the present invention is to establish a process whereby a retrovirus vector for specifically transferring foreign genes including those affecting cells into target cells over a broad range and expressing the genes therein can be stably produced at a high titer by strictly regulating, compared with the conventional processes, cytotoxic virus structural proteins and vector DNA with a cytotoxic or cell-affecting protein; to establish a process for elevating the recovery yield of a retrovirus vector by inhibiting the reinfection of producing cells with a pseudotyped retrovirus vector; and to efficiently screen high-expression cell clones by using a low-efficient drug resistance gene or a short-lived transcript drug resistance gene in the transcription of two genes by a recombinase with the use of the same promoter.

Delete the paragraph spanning pages 6 and 7 and insert the following therefor:

A DNA wherein an loxP sequence, a drug resistance gene, a polyA addition signal, an loxP sequence, a VSV-G gene and a polyA addition signal are arranged in this order in the downstream of a potent promoter is transferred into cells having gag and p01 genes of a retrovirus transferred thereinto. Then the resultant cells are screened with the use of the drug to prepare prepackaging cells. The prepackaging cells thus prepared are transduced with a retrovirus vector containing a desired gene inserted in its vector DNA to thereby transfer the gene into the prepackaging cells. At the same time, a recombinase is introduced to the cell. Thus, the VSV-G gene product

can be expressed at a high level within a short period of time with the use of the same potent promoter as the one employed for expressing the drug resistance gene. As a result, a pseudotyped virus vector having a high titer can be successfully prepared in a large amount prior to the appearance of the cytotoxicity of both the VSV-G gene product and foreign gene product in vector DNA. The present invention has been thus completed.

Page 24, delete the first full paragraph and insert the following therefor:

The virus titer is measured in the following manner. One day before the infection, rat fibroblasts 3Y1 are transferred into a 96-well plate to give a cell density of  $1.5 \times 10^{+3}/96$  wells. Samples are thawed and diluted with the liquid culture medium at various levels. Then the rat fibroblasts 3Y1 are transduced therewith together with 0.5 [mg]  $\mu\text{m}/96$  wells of polybrene. After three days, the infected cells are fixed with 1.25 % glutaraldehyde and the lacZ-transduced cells are stained by using X-gal in accordance with the method described above. The colonies thus stained blue are counted and it is confirmed that the colony count varies depending on the dilution level, thus calculating the titer. The titer is expressed in the number of the infectious units (hereinafter referred to simply as i.u.) per ml, namely, i.u./ml.

Page 30, delete the Table and insert the following therefor:

Antibody dilution level / Antibody	1/10	1/100	1/1000	No anti-body
anti-VSV-G antibody ([New Jersey] Indiana type)	<10	$3.0 \times 10^2$	$1.4 \times 10^3$	$3.3 \times 10^3$
anti-VSV-G antibody (New Jersey type)	$3.2 \times 10^3$	$2.8 \times 10^3$	$2.8 \times 10^3$	$3.3 \times 10^3$

Page 58, delete the paragraph beginning on line 3 and insert the following  
therefor:

A liquid culture medium containing  $1 \times 10^6$  i.u./ml of this adenovirus vector was treated with a rabbit polyclonal antiadenovirus antibody (assigned by Dr. Shiraki, Department of Virology, The Institute of Medical Science, The University of Tokyo) bonded to Protein G Sepharose (mfd. by Pharmacia) [four times each] for one hour at 4°C. Then the supernatant was taken up and an attempt was made to detect the adenovirus by using 293 cells similar to the above case. The 293 cells showed no denaturation within 12 days following the infection, which indicated that the adenovirus vector contained in the liquid culture medium had been completely eliminated by this antibody.